Modulation of Spinal-cord Function by Anesthesia

In recent years, much effort has been directed to studies designed to demonstrate the major central nervous system sites of action of general anesthetic agents. Some of these studies, concerned with the spinal cord, have demonstrated a role for spinal mechanisms in anesthetic action.

Single-unit recording within the spinal cords of experimental animals has revealed that those neuronal layers in the dorsal horn responding to noxious stimulation are sensitive to general analgesic agents. Neuronal layers unresponsive to noxious stimuli are relatively unaffected by analgesic agents. Since comparable anatomic arrangements of neurons are present in the human spinal cord, it is reasonable to suppose that a portion, at least, of the analgesic effect of general anesthetic agents is due to a suppressive effect upon the activity of spinal interneurons. There are at least two possible mechanisms for this suppressive effect. One mechanism would involve the direct action of the analgesic agent upon the interneuronal membrane: in short, a postsynaptic effect. Another mechanism that has been suggested is the possible enhancement by general anesthetics of presynaptic inhibition.

Inhibition of dorsal root input from cutaneous afferents and from muscle afferents in experimental animals is indicated by a slow potential appearing on the dorsal roots. The major negative dorsal root potential (DRP), thought to be produced by active depolarization of the branches of dorsal root axons within the spinal cord, is conducted passively into the dorsal roots through the cable properties of the dorsal root fibers.

Reflex and sensory afferent inhibition occurs with a time course closely similar to that of DRP, which is thus thought to be a sign of presynaptic inhibition.

It is also possible to record from the surface of the spinal cord a potential whose time course corresponds closely to that of DRP. This potential, in part, is produced by the same presynaptic depolarization mechanism as DRP, but for reasons relating to the placement of electrodes it is positive rather than negative.

An almost maximal DRP is produced by a low-intensity electrical stimulus that excites only large myelinated fibers in the peripheral nerve. Some controversy exists concerning the recordable events following an increase in stimulus intensity exciting smaller myelinated and unmyelinated fibers in the peripheral nerve sufficient to produce pain in experimental animals and in man. It is claimed by some that a positive, rather than a negative, dorsal root potential is produced by stimulation of small myelinated and unmyelinated fibers. This would suggest removal of presynaptic inhibition and facilitation of presynaptic input. It appears, however, that positive dorsal root potentials are not necessarily produced only by stimulation of small myelinated and unmyelinated fibers. Also, stimulation of small myelinated and unmyelinated fibers may produce a large negative dorsal...
root potential. When the entire fiber spectrum of a peripheral nerve is stimulated, two large negative dorsal root potentials appear in sequence, separated by the appropriate time delay required for the conduction of impulses in the unmyelinated fibers. Similarly, first one and then two positive waves would be expected to appear upon the surface of the spinal cord dorsum as the intensity of peripheral nerve stimulation increases. Such bimodal lumbar-sacral dorsal root potentials and dorsal cord potentials are found in the spinal animal and in the intact animal anesthetized with chloralose. In the chloralose-anesthetized animal they are maximal with low intensities of stimulation, as would be expected when an anesthetic with convulsant properties, such as chloralose, is used. The second of the two dorsal root potentials is labile, does not correlate well with the dorsal cord potential, and is not present when the spinal cord is sectioned at CI. It has not been determined whether, in the intact chloralose-anesthetized cat, the second component of the dorsal root potential is produced by a reverberating, evoked, phasic effect through a long supraspinal pathway, or whether chloralose unMASKS a tonic facilitation from supraspinal levels upon intraspinal mechanisms, without a recurrent loop.

Shimoji and his associates have developed a useful technique for the recording of evoked responses from the human spinal cord dorsum, using an epidural catheter as a recording electrode and processing the resultant signal with a digital computer. They demonstrate the presence of a positive spinal epidural evoked potential elicitable with low levels of electrical stimulation delivered to the periphery. This potential is comparable to the dorsal cord potential of experimental animals, which, in turn, corresponds well to DRv. The potential in man was found to be relatively stable during thiopental anesthesia and in slow-wave sleep.

The authors further demonstrate a bimodal positive spinal epidural evoked potential, the second component of which arises following increased intensity of stimulation. This second component of the epidural potential arising in man appears to be similar to that of the dorsal cord potential appearing in the chloralose-anesthetized cat, in that it is suppressed by barbiturate. It differs, however, in that the effect in the chloralose-anesthetized cat occurs at low intensities of stimulation.

The second component of the epidural potential in man disappears with the onset of slow-wave sleep. This may reflect a number of supraspinal effects, as Shimoji and his associates have postulated. Among these effects are reduction of tonic facilitation of spinal mechanisms for the production of the dorsal root potential, or production of a tonic inhibition of these mechanisms. From experiments in the cat, however, it appears that rostral spinal transmission is not interrupted during slow-wave sleep. Thus, it would be of interest to follow the changes in the various components of the evoked dorsal cord potential during the REM phase of desynchronized sleep where transmission is blocked.

The transmitter responsible for the dorsal root potential or its various components has not been identified, but may very well be similar to gamma-aminobutyric acid (GABA), since it is partially blocked by picrotoxin and by bicusculine. A second component of the dorsal root potential is, however, enhanced in animals treated with bicusculine and is abolished by treatment with barbiturate, as is the second component of the epidural potential in man. In ketamine-treated rabbits, Shimoji et al. show that the second component of DRv is eliminated by spinalization, as is the second component of DRv in bicusculine-treated cats.

Taking the data together, it appears that two forms of presynaptic depolarization occur in experimental animals, and probably in man. The first form, reflected in the first component of the dorsal cord potential, is independent of the existence or the state of activity of supraspinal structures, is enhanced by thiamylal, and is suppressed by ketamine and bicusculine. It is probably mediated by GABA. The second form, reflected in the second component of the dorsal cord potential, probably requires increased stimulus intensity for its production, is dependent upon supraspinal structures, is suppressed by thiamylal, and is facilitated or unaffected by bicusculine or by ketamine. This suggests different loci on the
dorsal root fibers for the two effects, different pathways, both spinal and supraspinal, and/or different transmitters.

In single-unit studies in spinal cats, ketamine has been found to suppress single units in those dorsal horn laminae concerned with the processing of information related to noxious stimuli.15,16 Barbiturates, on the other hand, have a tendency to suppress all dorsal horn laminae tested.17 The work of Shimoji et al.18 suggests that the release of, or at least the noninterference with, a spinal presynaptic inhibitory mechanism dependent upon supraspinal function may be yet another mechanism by which ketamine acts at the spinal level.

Shimoji and his co-workers12 are to be credited with the development and utilization of a technique that makes it possible to extend the results of studies in experimental animals to man. The ultimate effect of these studies will be to enhance our understanding of the effects of anesthetic agents exerted at the spinal level.

ARTHUR TAUB, M.D., PH.D.
Professor of Clinical Anesthesiology
and Lecturer of Neurology
LUKE M. KITAHATA, M.D., PH.D.
Professor and Chairman,
Department of Anesthesiology
Yale University
School of Medicine
New Haven, Connecticut 06510

References